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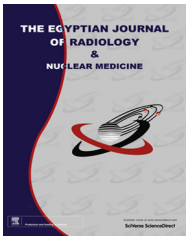

ORIGINAL ARTICLE

The role of apparent diffusion coefficient (ADC) value in the differentiation between the most common pediatric posterior fossa tumors

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KEYWORDS

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Abstract *Background:* Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) map provide information on MRI about the cellularity of the tumor and have an important role in the pre-operative differentiation of different tumor types.
Aim: Is to evaluate the role of ADC value measurement in the differentiation between the most common pediatric posterior fossa tumors which include juvenile pilocytic astrocytoma, ependymoma and medulloblastoma.
Patients & methods: Thirty patients were retrospectively included in this study. They were referred from the Neurosurgery Department and all of them suspected to have posterior fossa SOL according to the contrast enhanced CT. All patients were subjected to conventional MRI followed by diffusion MR imaging and calculation of the ADC values.
Results: In JPA (group 1, $n = 14$), ADC values ranged between 2.4 and 1.3×10^{-3} mm^2/s, ependymoma (group 2, $n = 9$), ADC values ranged between 1 and 1.3×10^{-3} mm^2/s and medulloblastoma (group 3, $n = 7$), ADC values ranged between 0.5 and 0.9×10^{-3} mm^2/s. Statistically significant

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difference in ADC value was detected between group1, group 2 and group 3, while no statistically significant difference was detected between group 1 and group 2.

Conclusion: The calculation of ADC value in the solid enhancing portion of a tumor is a simple and reliable technique for preoperative differentiation of the most common posterior fossa.

1. Introduction

Infratentorial intra-axial masses that occur in the cerebellum or the brain stem are distinctly different in the pediatric and adult population. Approximately 65% of all pediatric tumors arise in the posterior fossa. The most common neoplasms in children are the pilocytic astrocytoma, medulloblastoma, ependymoma, and brain stem glioma. In children, MRI and CT findings are used in combination with the location of the tumor, as well as the patient's age and sex may reliably predict tumor histology in more than 70% of cases (1).

Although MR imaging is essential for diagnosis and evaluation of the brain tumors, it offers limited information regarding the tumor type and grading. Diffusion-weighted (DW) MR imaging has enabled us to obtain additional information derived from microscopic motion of the water proton, which is not available by using conventional MR imaging. DW imaging has been applied for the assignment of tumor grades or differentiation of tumor types, as well as for the diagnosis of other brain SOLs (2). Recent studies evaluated the role of diffusion weighted imaging (DWI) in differentiating grade and type of pediatric brain tumors in the posterior fossa (3).

Measurement of the ADC would be expected to be useful in tumor assessment because variations in water content and diffusivity, which can be found in tumors for various reasons (e.g. vasogenic edema), likely provide information that is not readily available from conventional MR imaging (4).

Cellularity of tumors is defined as the number of cells in a given area of the tumor tissue. Water diffusion in the biological tissue is highly dependent on the ratio of extracellular to intracellular space. Furthermore, water diffusion is greater in extracellular space compared with that in the intracellular space. Therefore, an increase in cellularity, which would decrease the fraction of extracellular space, would also result in more restricted water diffusion (5).

The intranuclear water may have a higher diffusion coefficient than has cytoplasmic water. Water diffusivity is also suggested to be higher in the nucleus compared to that in the cytoplasm owing to decreased molecular crowding. These studies would suggest that tumors with a high nuclear to cytoplasmic ratio (N/C ratio) would actually have higher (rather than lower) ADC values. (5).

Tumors with a high N/C ratio tend to have a relatively small amount of extracellular matrix, because there is increased number of cells per tissue area. Tumors with a smaller extracellular compartment would be expected to have lower ADC values than tumors with a larger extracellular compartment. The amount of extracellular matrix is likely more important than the minor diffusivity difference between nucleus and cytoplasm. Therefore, in tumors with high cellularity (increased N/C ratio but reduced extracellular matrix) the measured ADC value is actually decreased (5,6).

The assessment of water diffusion in tissues is a complicated issue, which is affected by the viscosity of the medium, barriers to diffusion between compartments, molecular crowding, and the presence of active transport, bulk flow in capillaries, and the length of diffusion observation. The cellularity of the tumors likely contributes to the barriers to diffusion and molecular crowding but not necessarily to the other factors (6).

Absolute ADC values of contrast-enhancing solid tumor regions in children showed that ADC values were significantly higher in pilocytic astrocytomas than in ependymomas and medulloblastomas (7). ADC of ependymomas was higher than that of PNETs, and there was no overlapping. Since the ADC of ependymomas was consistently higher than 1×10^{-3} mm^2/s and that of PNET was consistently lower than 1×10^{-3} mm^2/s, it is suggested that preoperative determination of the ADC of fourth-ventricle tumors makes the differential diagnosis possible between ependymomas and medulloblastomas (8). Medulloblastomas show increased signal intensity within the tumor on DWI and low ADC values, which is associated with densely packed cells in the histological specimen. (9).

2. Patients and methods

The study was conducted in the Radio-diagnosis Department-Zagazig University in the time frame of November 2010–November 2011, and included 30 patients referred from the Neurosurgery Department. All of them were suspected to have posterior fossa tumor according to CT findings. Their age ranged from 6 months to 6 years. The patients were subjected to the following:

3. 1-Clinical history taking

3.1. 2-Mr examination

3.1.1. (A) Conventional MRI

All MRI studies were done using Philips Achieva class IIa machine (01.5 Tesla) with a protocol that included non contrast T1WI in axial and sagittal planes, axial and coronal fast spin echo T2WI, axial fluid attenuated inversion recovery (FLAIR) and post contrast axial, coronal and sagittal T1WIs.

3.1.2. (B) Diffusion weighted MR imaging (DWI)

The imaging sequence for DWI was a multi-section single shot spin echo EPI sequence (TR/TE/NEX: 4200/140 ms/I) with diffusion sensitivities of b values = 1000 s/mm^2. The diffusion gradients were applied sequentially in three orthogonal directions (X, Y & Z directions). Sections of 5 mm thickness, inter-slice gap of 1 mm, FOV 240 mm and a matrix of 128×256 were used for all images. The total acquisition time was 80 s.

Table 1 DWI findings, ADC ratio and values in the three examined posterior fossa tumor groups.

	JPA (group 1)		Ependymoma (group 2)		Medulloblastoma (group 3)	
No (%)	14 (46%)		9 (30%)		7(23%)	
SI on DWIs (*b*0)	High		High		High	
SI on DWIs (*b*1000) value	Low(cystic) SI (8 cases) Iso-slightly high SI (solid mural nodule) (6 case)		Heterogeneous SI		Predominantly high SI	
Range of ADC (10^{-3} mm^2/s) – Mean ADC value	2.4–3.1	2.1	1.01–1.3	1.0	0.55–0.95	0.57
		2.4		1.0		0.59
		2.9		1.3		0.93
		3.1		1.2		0.95
		2.2		1.2		0.91
		2.8		1.0		0.58
		2.4		1.3		0.55
		2.7		1.2		
	1.3–2.08			1.0		
		1.4				
		1.3				
		1.3				
		1.5				
		1.7				
		1.9				
		1.6				

JPA = juvenile pilocytic astrocytoma, SI = signal intensity.
N.B. The mean ADC value for the normal brain was 0.78 in JPA cases, 0.79 in ependymoma, 0.78 in medulloblastoma cases and 3 in CSF.

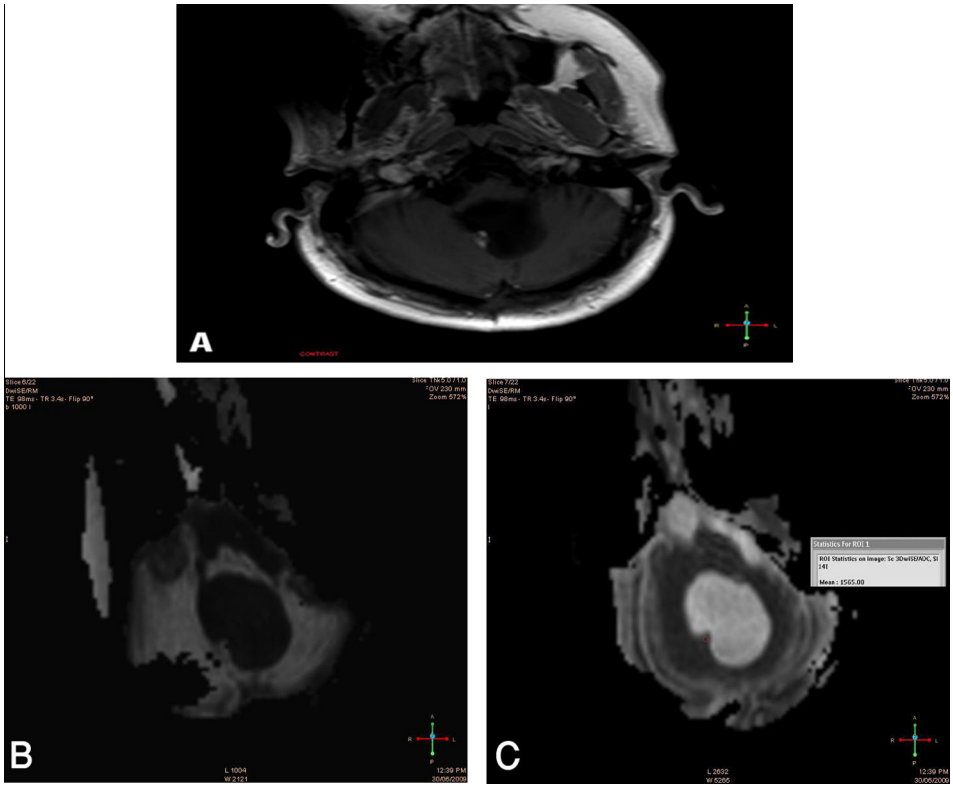

Fig. 1 A-Axial T1WI post Gd DTPA revealed midline infra-tentorial cystic SOL with enhanced peripherally located solid mural nodule. B-Axial DWI revealed a low signal intensity of the cystic lesion which displayed a CSF like signal, consistent with the lack of diffusion restriction. C-Axial ADC map revealed a hyperintense signal of the cystic lesion with ADC value = 1.5×10^{-3} mm^2/s raising the diagnosis of pilocytic astrocytoma.

Three types were obtained; orthogonal images, trace images and ADC maps. The ADC maps were calculated automatically by MRI software and included in the sequences. Measurements of ADC were made in regions of interest (ROIs) (enhancing solid portion of the lesion after it was identified on post contrast axial, coronal and sagittal T1 WIs and in the normal brain tissue). The ADC values were expressed in 10^{-3} mm^2/s.

(C) Histological diagnosis was provided by analysis of post-operative specimens.

(D) ADC values and ratios of JPAs, medulloblastomas, and ependymomas were compared by using a 2-tailed *t* test and one-way analysis of variance (ANOVA). The observed differences were considered statistically significant if *p* was less than .05.

4. Results

According to the conventional MR findings, the most common pediatric posterior fossa tumors encountered in our study were pilocytic astrocytoma in 14 cases(group 1), ependymoma in 9 cases(group 2) and medulloblastoma in 7 cases(group3), however, some diagnostic overlap had occurred between some ependymomas and medulloblastomas (in 4 cases) as the exact relation of the tumor to the forth ventricle cannot be assessed accurately on conventional MRI as well as between pilocytic astrocytomas and medulloblastoma (in 2 cases) because of atypical conventional MRI findings in 2 cases of pilocytic astrocytoma (Table 1).

In the examined juvenile pilocytic astrocytomas (group 1, $n = 14$), the cystic component in all cases of JPA appeared hyperintense on DWIs ($b0$), and hypointense on DWIs ($b1000$) (Table 1) compared to normal appearing brain parenchyma, denoting free diffusion. Their ADC values ranged from $2.4–3.1 \times 10^{-3}$ mm^2/s. The solid mural nodule of the tumor displays iso-to hyperintense signal on DWI ($b1000$) and iso to hypointense signal on ADC map denoting restricted diffusion in the solid mural nodule in JPA, the ADC value was between 1.3 and 2.08×10^{-3} mm^2/s (Fig. 1).

In the examined ependymoma 9 cases (group2, $n = 9$), the signal intensity was heterogeneous on both DWI and ADC map due to the presence of solid and cystic components (Table 1). The solid enhanced component displayed iso-to slightly hyperintense signal on DWI, hypointense signal on ADC map and had ADC value between 1.01 and 1.3×10^{-3} mm^2/s (Fig. 2) suggesting restricted diffusion more than that seen in JPA cases.

In medulloblastoma cases (group3, $n = 7$), the diffusion was significantly restricted relative to JPA and ependymoma due to characteristic densely packed cells. All of them appeared predominantly hyperintense on DWI relative to the normal brain parenchyma, hypointense on ADC map and had ADC value ranged between 0.55 and 0.9×10^{-3} mm^2/s, which is consistent with marked restriction of diffusion (Fig. 3).

There were significant differences in the ADC values between groups 1 and 3, and between groups 2 and 3 ($p = 0.000$) (Table 2). However no statistically significant differences between group 1 and 2 ($p > 0.05$) were detected (Table 2). There was no overlap in individual tumor ADC values or ratios between JPA and medulloblastoma (Fig. 4).

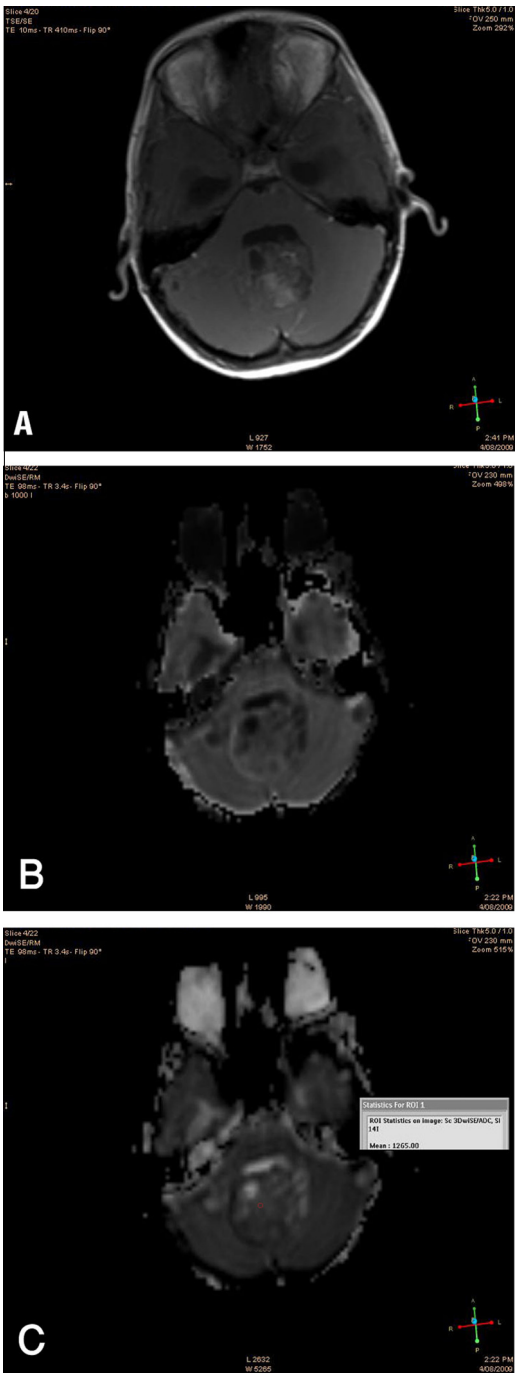

Fig. 2 A-Axial T1WI post Gd DTPA showing a heterogeneously enhanced midline posterior fossa SOL, posterior to the 4th ventricle. The diagnostic possibilities were medulloblastoma versus ependymoma. B-Axial DWI revealed high SI of the lesion relative to the CSF, mainly in its central part which is consistent with diffusion restriction. C-Axial ADC map revealed a low signal intensity of the lesion relative to the CSF with ADC value = 0.7×10^{-3} mm^2/s denoting marked diffusion restriction and supporting the diagnosis of medulloblastoma.

5. Discussion

Diffusion MR imaging is a technique in which dedicated phase-defocusing and refocusing gradients allow evaluation

Fig. 3 A-Axial T1WI postGd DTPA revealed the midline posterior fossa SOL with heterogeneous pattern of enhancement, sparing peripheral cystic areas. B-Axial DWI revealed an intermediate signal intensity of the lesion denoting restricted diffusion with CSF like signal intensity of the cystic areas which is consistent with no diffusion restriction. This finding raised the possibility of ependymoma, however, medulloblastoma cannot be ruled out. C-Axial ADC map revealed a low signal intensity of the lesion relative to the CSF denoting diffusion restriction with ADC value = 1.1×10^{-3} mm^2/s which is in the ADC range of ependymoma.

Table 2 Multiple comparisons between the ADC values in the three groups.

(I) GROUP	(J) GROUP	Mean Difference (I-J)	Sig.
1.00	2.00	.12437	.287
	3.00	.68651	.000*
2.00	1.00	−.12437-	.287
	3.00	.56214	.000*
3.00	1.00	−.68651-	.000*
	2.00	−.56214-	.000*

* Statistically significant p value < 0.05.

of microscopic water diffusion within tissues, where calculated ADC maps represent an absolute measure of average diffusion for each voxel (3).

In our study, the DW MR imaging was performed using echo-planar units, and because of its sensitivity to alterations in the motion of water molecules in the region of the brain studied, it had a significant impact on clinical imaging.

Tumor cellularity and tumor grade had been correlated with ADC values from the ADC maps (the ADC value is inversely proportional to the tumor cellularity). Primary brain tumors with higher cellularity or higher grades typically have lower ADC values when compared with normal brain tissues (10).

In our study, JPA and medulloblastoma could be differentiated on the basis of ADC value in all patients and there was no overlap in the obtained measurements between the two tumor types. The ADC value was higher than 1.3×10^{-3} mm^2/s in JPA cases (the cystic component showing ADC values 2.4–3.1×10^{-3} mm^2/s and the solid enhanced component showing ADC values 1.3–2.08×10^{-3} mm^2/s) while in medulloblastoma cases the ADC values ranged between 0.55 and 0.9×10^{-3} mm^2/s, indicating a statistically significant difference in the ADC values between the two tumor types, in consistent with *Rumboldt* et al. (7), as they concluded that significant differences in cellularity of pediatric cerebellar neoplasms, particularly between JPAs and medulloblastomas indicate that these lesions could potentially be distinguished by their ADC values. They used cutoff values of more than 1.4×10^{-3} mm^2/s for JPA and less than 0.9×10^{-3} mm^2/s for medulloblastoma which seem to reliably provide the diagnosis which may affect the treatment plan and prognosis.

These findings in JPAs and medulloblastomas are probably secondary to the low cellularity and relatively small nuclear area typically seen in the former tumor types in contradistinction to the densely packed cells and large nuclei characteristic for the latter (8).

Ependymomas are well circumscribed, moderately cellular tumors. The typical cellularity in posterior fossa ependymomas therefore is somewhere between that of astrocytomas and medulloblastomas (12).

In this study, the ADC values also clearly distinguished medulloblastoma from ependymoma in all patients, again without any overlap as most ependymoma cases showed ADC values 1.01–1.3×10^{-3} mm^2/s which are higher than that seen in medulloblastoma in consistent with Yamasaki et al.

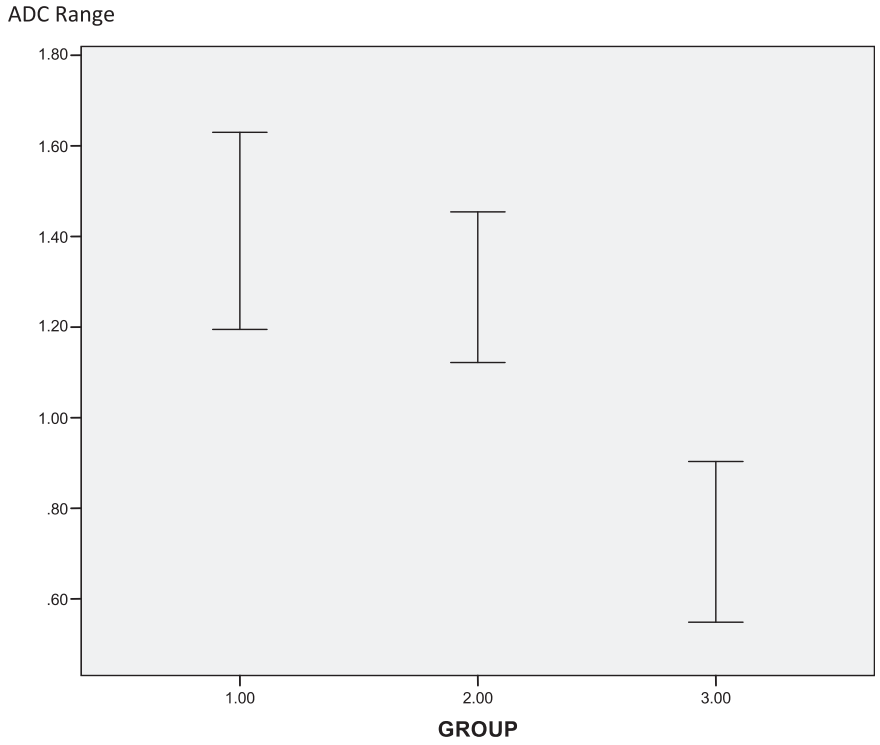

Fig. 4 Scatter diagram representing the ADC value in the three tumor types is included in this study. The ADC value is expressed in 10^{-3} mm^2/s.

(13), as they found that ADC values were retrospectively 100% accurate in the differentiation between ependymomas and medulloblastomas.

Also the ADC values of JPAs were also higher from ependymomas in our study and this difference was not statistically significant ($p = <$) because of ADC value diagnostic overlap between the two tumor types in disagreement with other authors (7), they found that ependymomas were also significantly different from other tumor types and in most of cases show ADC values $1.00–1.30 \times 10^{-3}$ mm^2/s.

Moreover, Gauvain et al. (11) found in their study of posterior fossa tumor cases, a good correlation between ADC ratio (Tumor ADC: Normal brain ADC) and tumor classification. In addition the absolute ADC values and tumor cellularity/total nuclear area also correlated well.

On the other hand Jaremko et al. (14), found overlap in ADC values between different tumor types was explained not only by technical factors (in small, heterogeneous, calcify, or hemorrhagic tumors), but also likely reflected true histological variability, given that there were three overlap cases included a desmoplastic medulloblastoma, an anaplastic ependymoma, and a JPA with restricted diffusion in its nodule.

Based on our results, we suggest that ADC values may play a potentially important role in the pre-operative management of children with posterior fossa tumors. If high ADC value is detected, a patient may go directly to surgery without additional imaging as pilocytic astrocytoma is unlikely to metastasize via CSF seedling. On the other hand, very low ADC value suggests that the tumor is medulloblastoma, so imaging of the spine is essential to exclude metastases and appropriately stage the patient.

6. Conclusion

ADC value is a simple and available technique for evaluation of pediatric cerebellar neoplasms and accurately differentiate between the most common tumor types, JPA, ependymoma and medulloblastoma.

Cutoff values of more than 1.3×10^{-3} mm^2/s that are characteristic of JPA and less than 0.9×10^{-3} mm^2/s of medulloblastoma seem to provide the diagnosis which may guide further diagnostic studies, treatment planning and outcome.

Ependymoma is also significantly differentiated from medulloblastoma, but no statistically significant difference between ependymoma and JPA was detected.

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